Mitochondrial Metabolism in hESC and hiPSC Differentiation, Reprogramming, and Cancer

Grant Award Details

Mitochondrial Metabolism in hESC and hiPSC Differentiation, Reprogramming, and Cancer

Grant Type: Basic Biology I

Grant Number: RB1-01397

Project Objective: to characterize mitochondrial metabolism in human pluripotent stem cells (hPSC) and understand relationships between mitochondrial regulation and the control of stem cell function

Investigator:

Name:	Michael Teitell
Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $1,323,029

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Mitochondrial Metabolism in hESC and hiPSC Differentiation, Reprogramming, and Cancer

Public Abstract: Stem cell quality and safety in developing regenerative medicine therapies is of utmost importance. Poor outcomes include inadequate functionality, exhaustion, immune rejection, cancer development, and others. Recent studies strongly support our core hypothesis that mitochondrial function determines stem cell quality and safety. Dysfunctional mitochondria foster cancer, diabetes, obesity, neurodegeneration, immunodeficiency, and cardiomyopathy. Unlike whole genome approaches, methodological hurdles for evaluating mitochondria in human embryonic stem cells (hESCs) and in reprogrammed human induced pluripotent stem cells (hiPSCs) are significant and techniques developed or adapted for stem cells are almost non-existent. With a 2-year CIRM Seed Grant, we developed new approaches for analyzing respiration (oxygen consumption that drives energy production) in hESCs in a series of 4 invited publications for the stem cell scientific community (www.JoVE.com; 2008). A manuscript describing the function of hESC mitochondria in low oxygen (hypoxia), in normoxia (room air), and during differentiation is in final preparation. We also collaboratively developed small molecule inhibitors of specific mitochondrial functions, thereby providing new essential tools to the scientific community for interrogating the function of stem cell mitochondria. Unlike current inhibitors of mitochondrial function, with are generally non-specific, irreversible, and toxic over time, our novel inhibitors are reversible, non-lethal, and target a range of specific mitochondrial functions. These inhibitors are undergoing continuous molecular refinement and validation studies for use in basic studies and can potentially lead to insights for clinical application in common diseases, such as diabetes and cancer. These advances form the underpinnings for our current proposal.

We now propose two main aims to address fundamental questions in mitochondrial biology and safety of stem cells. In Aim 1, we have identified two lead candidate mechanisms for regulating oxygen utilization and energy production in stem cell mitochondria. It is known that reduced levels of the proteins that regulate energy production favor the development of cancer. We will determine the functionality of energy producing pathways in hESC, hiPSC, normal cell, and cancer cell mitochondria. In Aim 2 studies, we will utilize our novel mitochondrial inhibitors to determine which additional functions are essential to derive safe stem cells for clinical development. We also embark on a focused discovery protocol, based on already established genome-wide methods for stem cells, to identify key regulators of mitochondrial maturation with stem cell differentiation. Combined, our studies build upon successful CIRM-funded work to move into functional analyses of mitochondria that support stem cell self-renewal, survival, and differentiation, with major economic and social implications for new-age cellular therapies in medicine.

Statement of Benefit to California:	Our proposal benefits the people and state of California by adding new essential knowledge on the mitochondrial functions of human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), and their lineage differentiated derivatives, in support of the California peoples' and taxpayers' commitment to personalized cell therapies. This new work builds on a highly successful two-year CIRM Seed Grant,[REDACTED], that provided one of the first systematic characterizations of stem cell mitochondria. CIRM funds supported 1) four published protocols (www. JoVE.com; 2008) on growing pure stem cells and methods of characterizing mitochondria for the scientific community, 2) the first report of high-resolution genome differences between hESCs derived from different individuals (Stem Cells; 2008), and 3) now almost complete studies that characterize the functional capabilities of hESC mitochondria that are being prepared for publication(s). This CIRM-supported comprehensive characterization of stem cell mitochondria function , and new mechanism- and discovery-driven studies in our current proposal, will help guide clinicians and scientists to select the best possible stem cells for investigation and use. Our ongoing work will propel therapy development in California's major academic centers and will provide information to many of California's biotechnology and pharmaceutical companies in the ever growing stem cell industry, whose success will propel hiring and increased economic prosperity for the state. Results from these studies will provide additional information to patient advocates, ethicists, and medical geneticists to help select the optimal course for developing and modifying stem cell usage policies and infrastructure within California. This proposal will also provide new information for patients and their physicians that may, at some future time, impact the selection of particular stem cells with specific mitochondrial attributes for specific types of therapeutic applications. In sum, added knowledge provided by our proposed studies on mitochondrial factors that control stem cell metabolism and mitochondrial maturation will help define and drive successful methods of hESC and hiPSC differentiation, will identify the most completely reprogrammed hiPSCs from a metabolic standpoint, and will generate cell therapies with reduced risk, increased safety, and limited cancer potential. With success tangible health and economic impact on California, its academic institutions and biotechnology/pharmaceutical companies, and the rest of the nation will be achieved as California and its people lead the way forward with personalized medicine for the 21st century and beyond.